

Resveratrol Revelations

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The "French Paradox" is not a political conundrum, but rather an idiom, used to express the initial surprise of Western epidemiologists as to the apparent contradiction of the juxtaposition of a high-fat diet and the comparatively low incidence of heart disease in the population of France.¹

Although there are several plausible explanations, including the moderate use of alcohol itself, it appears that the abundant supply of *polyphenols* found in red wine is part of the answer to this "riddle."² Polyphenols are a major class of plant nutrients known as phyto-nutrients, which are chemicals found in plants (phytochemicals). There are tens of thousands of phytochemicals, but comparatively few appear to be useful in promoting optimal health in human beings. Polyphenols can be further divided into subclassifications such as anthocyanins and flavonoids, the former of which contains the stillbenes, of which the most well-known and researched is the topic of this "revelation": resveratrol.

Resveratrol is most abundant in vine fruits, especially red grapes; pine trees; peanuts; and most abundantly in *polygonum cuspidatum*, an Asian plant used for centuries for heart and liver ailments.

In the last decade of the 20th century, the search for a better understanding of the "French Paradox" led eventually to a plethora of scientific investigation of red wine polyphenols, and most especially, of resveratrol. This research led to the "resveratrol revelations," summed up with such descriptions as:

- powerful antioxidant;
- anti-proliferative, anti-atherosclerotic;
- anti-clotting;
- senescence preventive;
- central nervous system protective;
- anti-cancer cell protective;
- hormone, gene and enzyme modulator; and
- longevity activator.

Heart Helper

By now, almost everyone knows there is a connection between cardiovascular disease and cholesterol. Those of us with a bit more familiarity on the subject appreciate that the most damaging types of cholesterol are the low-density and very-low-density "fats/proteins" (the "bad" lipoproteins - LDL and VLDL). We also appreciate that it is only when these "bad" lipoproteins are oxidized by free radicals that they become the artery-clogging menaces for which they are feared. This is why it is thought that the water- and fat-soluble vitamins, such as C and E, appear to help prevent heart disease, as they each protect against certain free radicals that oxidize the bad "fats/proteins" in the blood. Resveratrol's own marked antioxidant activity is most fortuitously accompanied by its ability to:

- boost nitric oxide, an endogenous chemical that relaxes arteries;
- halt proliferation of the cells responsible for narrowing our arteries; and
- inhibit thrombin and a legion of other pro-clotting conspirators.³⁻⁷

Minding Your Memory

Like it or not, we are all "fatheads," in that our brains are composed most especially of fatty acids! Therefore, our minds, as much as our hearts, need antioxidant protection. Those suffering from Alzheimer's disease produce an abnormal protein, or more exactly, a peptide - the now infamous beta-amyloid. These pitiless peptides produce so much free-radical damage that the brain cells are slowly "burned" to death, leading to this universally dreaded dementia. Resveratrol, particularly when combined with vitamins C and E, provides the much-sought protection from these monstrous "mind-munchers."

It is even possible that resvera-trol will be used medicinally in therapeutic doses, following stroke and central nervous system ischemia and injury. Resveratrol injected into laboratory animals proved better than prednisone as a posttraumatic spinal-cord injury anti-inflammatory drug. Researchers speculate that regular supplementation may be neuroprotective, as well.⁸⁻¹³

Cancer Risk Reversal With Resveratrol

Recent research strongly suggests that resveratrol is a broad-spectrum cancer-inhibiting agent, and reveals that resveratrol:

- promotes programmed cell death (apoptosis);
- kills cancer cells, (both with and without tumor suppressor gene p53);
- increases vitamin D3's steroid- mediated inhibition of breast cancer;
- increases cancer cell vulnerability to chemotoxic agents (as in Hodgkin's lymphoma);
- inhibits cancer cell metastasis to bone, (especially for renal, breast and pancreatic carcinomas);
- inhibits cancers associated with high linoleic fatty acid Western diets (omega 6 EFA); and,
- concurrently protects healthy cells via its abilities as an antioxidant, and as a modulator of genes, hormones, enzymes and other endogenous (self-made) cell-signaling chemicals!^{14-25,}

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Long Live Resveratrol!

As wonderful as resveratrol sounds, I have saved the most exciting news for last. Just recently, scientists at Harvard Medical School and BIOMOL research labs discovered that this most remarkable phytonu-trient activates a "longevity gene" that increases the life span of yeast cells by 70 percent! This is not just good news for yeast cells; prior to this discovery, the only proven method of life extension was calorie restriction. But if calorie restriction is also to be "successful" for humans, it means being very skinny, tired and cold all the time - not to mention hungry! Sounds more like a life sentence than life extension for most of us!

Calorie restriction in yeasts, worms and flies occurs, at least in part, by activating a gene called sirtuin (SIR). The potential good news is that we have our own version of a "Methuselah gene," and resveratrol supplementation turns on (via deacetylation) our SIR, as well as calorie restriction!

Another theory of aging, the "waste accumulation theory," holds that we "suffocate in the ashes of our own metabolic fires." It is known that as we pass our prime, we lose our ability to perfectly replicate our DNA in every new cell. Slowly, these less-than-perfect copies accumulate, resulting in

what has been termed "junk DNA," whose debris eventually chokes optimal functioning. Resveratrol antioxidant power has been shown to protect oxidation of both cellular and mitochondrial DNA, thereby helping to minimize these errant copies that kill!³¹⁻³²

Resveratrol Reservations

Being a board-certified anti-aging specialist, I am well-aware of the desire in medical and nutritional ventures to find (and sell) the "magic bullet" that will stop aging. And while I am very excited to share this research on resveratrol, I feel strongly that health and aging are multifactorial and that no single "magic" elixir exists.

Having said that, I will close with some words about increasing resveratrol and polyphenol intake via diet and supplements. Polyphenols are richest in fruits in general; berries are generally the richest source of anthocyanins. Red wine polyphenol concentration depends on many factors, such as type, climate and soil. Even the best red wines may have little more than 2 mg per liter, but research in the scientific literature suggests that at least 10 times that amount (20 mg) is needed to begin to optimize the potential health benefits of resveratrol, and a hundred times that amount (100 to 200 mg) or more is required for actual potential therapeutic purposes.³³

Because resveratrol is highest in *polygonum cuspidatum*, combining this single phytonutrient in pharmaceutical grade with red wine, whole grape polyphenols (RWP), as naturally found in nature, is likely the best supplemental approach. Quercetin, another polyphenol especially abundant in green apple skins and onions, enhances viability.

As with most supplements, there is a great deal of variability in quality, quantity and activity. Unfortunately, as *Consumer Report*-type expose continually inform us, it is hard to tell what is in a bottle just by reading the label. Health professionals and laypersons alike should stay with high-quality companies of which they are familiar.

1. Gronback M, et al. Type of alcohol consumed and mortality from all causes, coronary heart diseases, and cancer. *Ann Intern Med* 2000;133:411-19.
2. Tadolini B, et al. Resveratrol inhibition of lipid peroxidation. *Free Radic Res* 2000;33:105-14.
3. Imonini G, et al. Emerging potentials for an antioxidant therapy as a new approach to the treatment of systemic sclerosis. *Toxicology* 2000;155:1-15.
4. Zou JG, et al. Effect of red wine and wine polyphenol resveratrol on endothelial function in hypercholesterolemic rabbits. *Int J Mol Med* 2003;11:317-20.
5. Haider UG, et al. Resveratrol increases serine 15-phosphorylated but transcriptionally impaired p53 and induces a reversible DNA replication block in serum-activated vascular smooth muscle cells. *Mol Pharmacol* 2000;363:925-32.
6. Zbikowska HM, et al. Antioxidants with carcinostatic activity (resveratrol, vitamin E and selenium) in modulation of blood platelet adhesion. *J Physiol Pharmacol* 2000;51:513-20.
7. Pace-Asciak CR, et al. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. *Clin Chim Acta* 1995;235:207-19.
8. Burkitt MJ, et al. Effects of trans-resveratrol on copper-dependent hydroxyl-radical formation and DNA damage: evidence for hydroxyl-radical scavenging and a novel, glutathione-sparing mechanism of action. *Arch Biochem Biophys* 2000;381:253-63.
9. Draczyska-Lusiak B, et al. Oxidized lipoproteins may play a role in neuronal cell death in Alzheimer disease. *Mol Chem Neurobiol* 1998;33:139-48.
10. Jang JH, et al. Protective effect of resveratrol on beta-amyloid-induced oxidative PC12 cell death. *Free Radic Biol Med* 2003;34:1100-10.
11. Chanvitayapongs S, et al. Amelioration of oxidative stress by antioxidants and resveratrol in PC12 cells. *Neuroreport* 1997;8:1499-502.

12. Yang YB, et al. Effects of resveratrol on secondary damages after acute spinal cord injury in rats. *Acta Pharmacol Sin* 2003; 24:703-10.
13. Sinha K, et al. Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. *Life Sci* 2002;71:655-65.
14. Cal C, et al. Resveratrol and cancer: chemoprevention, apoptosis, and chemosensitizing activities. *Curr Med Chem-Anti-Cancer Agents* 2003;3:77-93.
15. Pervaiz S. Resveratrol - from the bottle to the bedside? *Leuk Lymphoma* 2001;40:491-8.
16. Ding XZ, et al. Resveratrol inhibits proliferation and induces apoptosis in human pancreatic cancer cells. *Pancreas* 2002;25:e71-e76.
17. Gusman J, et al. A reappraisal of the potential chemopreventive and chemotherapeutic properties of resveratrol. *Carcinogenesis* 2001;22:1111-17.
18. Lu R, et al. Resveratrol, a natural product derived from grape, exhibits antiestrogenic activity and inhibits the growth of human breast cancer cells. *J Cell Physiol* 1999;179:297-304.
19. Serrero G, et al. Effect of resveratrol on the expression of autocrine growth modulators in human breast cancer cells. *Antioxid Redox. Signal* 2001;3:969-79.
20. Mitchell SH, et al. Resveratrol inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells. *Cancer Res* 1999;59:5892-5.
21. Narayanan BA, et al. Interactive gene expression pattern in prostate cancer cells exposed to phenolic antioxidants. *Life Sci* 2002;70:1821-39.
22. Pozo-Guisado E, et al. The antiproliferative activity of resveratrol results in apoptosis in MCF-7, but not in MDA-MB-231 human breast cancer cells: cell-specific alteration of the cell cycle. *Biochem Pharmacol* 2002;64:1375-86.
23. Wietzke JA, et al. Phytoestrogen regulation of a vitamin D3 receptor promoter and 1,25-dihydroxyvitamin D3 actions in human breast cancer cells. *J Steroid Biochem Mol Biol* 2003; 84:149-57.
24. Ulsperger E, et al. Resveratrol pretreatment desensitizes AHTO-7 human osteoblasts to growth stimulation in response to carcinoma cell supernatants. *Int J Oncol* 1999;15:955-59.
25. Nakagawa H, et al. Resveratrol inhibits human breast cancer cell growth and may mitigate the effect of linoleic acid, a potent breast cancer cell stimulator. *J. Cancer Res Clin Oncol* 2001;127:258-64.
26. Zhuang H, et al. Potential mechanism by which resveratrol, a red wine constituent, protects neurons. *Ann NY Acad Sci* 2003;993:276-86.
27. Floreani M, et al. Oral administration of trans-resveratrol to guinea pigs increases cardiac DT-diaphorase and catalase activities, and protects isolated atria from menadione toxicity. *Life Sci* 2003;72:2741-50.
28. Ferguson LR. Role of plant polyphenols in genomic stability. *Mut. Res* 2001;475:89-111.
29. Casper RF, et al. Resveratrol has antagonist activity on the aryl hydrocarbon receptor: implications for prevention of dioxin toxicity. *Mol Pharmacol* 1999;56:784-90.
30. Hsieh TC, et al. Cell cycle effects and control of gene expression by resveratrol in human breast carcinoma cell lines with different metastatic potentials. *Int J Oncol* 1999;15:245-52. Yen GC, et al. Effects of resveratrol and 4-hexylresorcinol on hydrogen peroxide-induced oxidative DNA damage in human lymphocytes. *Free Radic Res* 2003;37:509-14.
31. Revel A, et al. Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects lung from DNA damage and apoptosis caused by benzo[a]pyrene. *J Appl Toxicol* 2003;23:255-61.
32. Mitchell T. Resveratrol: cutting-edge technology available today. *Life Extension* November 2003:8-12.

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